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Efficient Aqueous-Phase Heck and Suzuki Couplings of Aryl Bromides Using Tri(4,6-dimethyl-3-sulfonatophenyl)phosphine Trisodium Salt (TXPTS)

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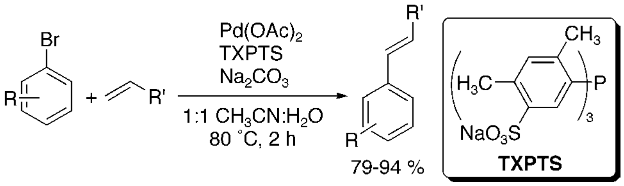
ABSTRACT



Sterically demanding, sulfonated arylphosphines TXPTS and TMAPTS have been applied to the aqueous-phase Heck and Suzuki coupling of aryl bromides. TXPTS provides good yields of Heck coupling products from aryl bromides at 80 °C, while both TMAPTS and TPPTS gave significantly less active catalysts. TXPTS is the first ligand to promote the aqueous-phase Heck coupling under such mild conditions. Both TXPTS and TMAPTS provide active catalysts for Suzuki couplings of aryl bromides at 50 °C.

Water continues to attract significant attention as an alternative solvent in organic synthesis due to its low cost, toxicity, and environmental impact. Water is particularly attractive in certain metal-catalyzed processes where a water-soluble catalyst can be separated from an organic product stream and potentially recycled.[1] Water-soluble ligands are commonly used to give hydrophilic catalysts that will be retained in the aqueous phase. The most commonly used water-soluble ligand is tri(3-sulfonatophenyl)phosphine (TPPTS), which was originally developed by Rhone−Poulenc for use in the aqueous-phase hydroformylation of propylene.[2]

TPPTS has been successfully used as a water-soluble replacement for triphenylphosphine in a variety of catalytic processes. TPPTS in combination with palladium has modest activity in the aqueous-phase Suzuki,[3] Heck,[3a,4] and Sonogashira[3a,4a,5] cross-coupling reactions. To date, these systems have been largely limited to couplings of aryl iodides, while couplings of aryl bromides have required high temperatures or activated substrates. Modest activity for aqueous-phase Suzuki couplings of unactivated aryl bromides has been observed recently using high catalyst loadings of Pd/TPPTS,[3c] while aqueous-phase Heck couplings of unactivated aryl bromides require high temperatures (100−150 °C).[6] The Suzuki coupling of activated aryl chlorides using a nickel/

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[1] (a) Genêt, J. P.; Savignac, M. *J. Organomet. Chem.* **1999**, *576*, 305−317. (b) Joó, F.; Kathó, Á. *J. Mol. Cat A. Chem.* **1997**, *116*, 3−26.

[2] Cornils, B.; Kuntz, E. G. *J. Organomet. Chem.* **1995**, *502*, 177−186.

[3] (a) Casalnuovo, A. L.; Calabrese, J. C. *J. Am. Chem. Soc.* **1990**, *112*, 4324−4330. (b) Genêt, J. P.; Linquist, A.; Blard, E.; Mouries, V.; Savignac, M.; Vaultier, M. *Tetrahedron Lett.* **1995**, *36*, 1443−1446. (c) Dupuis, C.; Adiey, K.; Charruault, L.; Michelet, V.; Savignac, M.; Genêt, J.-P. *Tetrahedron Lett.* **2001**, *42*, 6523−6526.

[4] (a) Genêt, J. P.; Blart, E.; Savignac, M. *Synlett* **1992**, 715−717. (b) Mirza, A. R.; Anson, M. S.; Hellgardt, K.; Leese, M. P.; Thompson, D. F.; Tonks, L.; Williams, J. M. J. *Org. Process Res. Dev.* **1998**, *2*, 325−331.

[5] (a) Amatore, C.; Blart, E.; Genêt, J. P.; Jutand, A.; Lemaire-Audoire, S.; Savignac, M. *J. Org. Chem.* **1995**, *60*, 6829−6839. (b) Dibowski, H.; Scmidtchen, F. P. *Tetrahedron Lett.* **1998**, *39*, 525−528.

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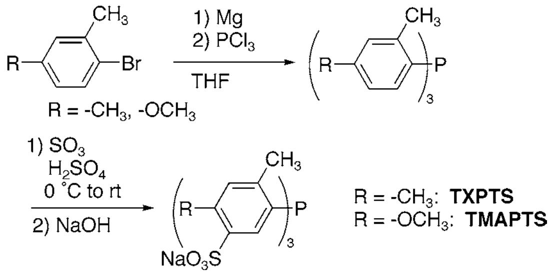
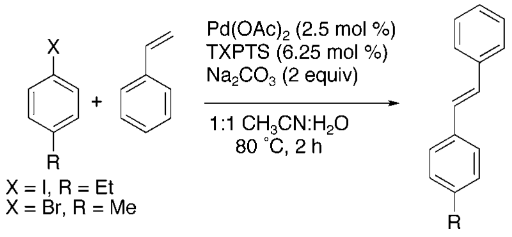
10.1021/ol0360288 CCC: $27.50

TPPTS catalyst system has also been reported.[7] Aqueous-phase couplings of aryl bromides using high loadings of ligand-free catalysts have also been reported in the presence of surfactants.[8] For this method to be more widely applicable, catalysts with improved generality for coupling of unactivated aryl bromide and chloride substrates under mild conditions must be identified. Although a variety of water-solubilizing groups have been appended to the triphenylphosphine structure,[6,9] little effort has been devoted to modifying the steric and electronic properties of water-souble arylphosphines. In contrast, electron-rich, water-soluble alkylphosphines with a range of cone angles have been prepared.[10]

Tri-*o*-tolylphosphine has been found to be superior to triphenylphosphine in many palladium-catalyzed cross-coupling reactions.[11] In an effort to identify more efficient ligands for aqueous-phase cross-coupling reactions, we have prepared sulfonated triarylphosphine ligands containing ortho substituents. The synthesis of tri(4,6-dimethyl-3-sulfonatophenyl)phosphine trisodium (TXPTS, Scheme 1) has been previously reported.[12] Tri(4-methoxy-6-methyl-3-sulfonatophenyl)phosphine trisodium salt (TMAPTS) was prepared in a similar fashion as a more electron-rich analogue of TXPTS. We have previously reported that TXPTS gave significantly more active catalysts than TPPTS for the Suzuki coupling of halogenated nucleosides.[13] Herein, we report the ability of TXPTS and TMAPTS to promote Heck and Suzuki couplings of simple aryl bromides.

Scheme 1. Synthesis of TXPTS and TMAPTS





(1)

The activity of catalysts TXPTS, TMAPTS, and TPPTS in combination with Pd(OAc)$_2$ were initially screened in the Heck coupling of 1-ethyl-4-iodobenzene and styrene at 80 °C (eq 1, Figure 1). The catalyst derived from TXPTS gave complete conversion to product in 2 h. TPPTS and TMATPS in combination with Pd(OAc)$_2$ gave approximately 30% yields of the stilbene product after 2 h, while Pd(OAc)$_2$ alone gave very little product. The screening was repeated with 4-bromotoluene under the same conditions. TXPTS/Pd(OAc)$_2$ again gave a good yield (77%) of stilbene product after 2 h at 80 °C. The catalysts derived from TMAPTS and TPPTS gave lower yields of the desired product (40 and 28%, respectively), while essentially no product was observed in the absence of ligand. To our knowledge, this is the first Heck coupling of unactivated aryl bromides to occur below 100 °C using water-soluble arylphosphine ligands.

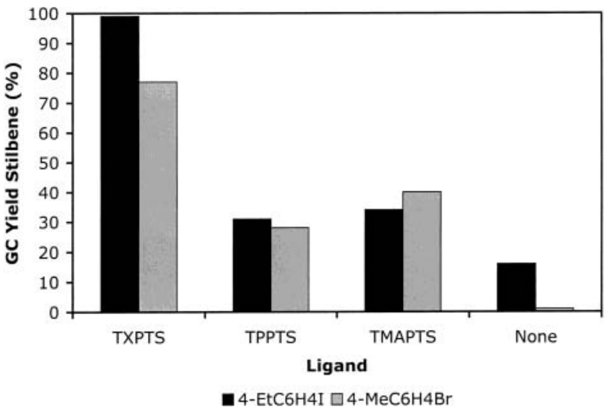


Figure 1. Comparison of GC yields for the Heck coupling of 1-ethyl-4-iodobenzene or 4-bromotoluene and styrene (eq 1).

The scope of the TXPTS/Pd(OAc)$_2$ catalyst system was explored using a series of aryl halides (Table 2). Coupling of 1-ethyl-4-iodobenzene and styrene gave 4-ethylstilbene in 90% isolated yield (entry 2). Good to excellent yields were also obtained in the coupling of aryl bromides and styrene to give substituted stilbenes. Both electron-donating and electron-withdrawing substituents gave excellent yields of

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(8) Arcadi, A.; Cerichelli, G.; Chiarini, M.; Correa, M.; Zorzan, D. *Eur. J. Org. Chem.* **2003**, 4080−4086.

(9) (a) Wasserscheid, P.; Waffenschmidt, H.; Machnitzki, P.; Kottsieper, K. W.; Stelzer, O. *Chem. Commun.* **2001**, 451−452. (b) Uozumi, Y.; Danjo, H.; Hayashi, T. *J. Org. Chem.* **1999**, *64*, 3384−3388. (c) Gelpke, A. E. S.; Veerman, J. J. N.; Goedheijt, M. S.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Hiemstra, H. *Tetrahedron* **1999**, *55*, 6657−6670. (d) Parisot, S.; Kolodziuk, R.; Goux-Henry, C.; Iourtchenko, A.; Sinou, D. *Tetrahedron Lett.* **2002**, *43*, 7397−7400.

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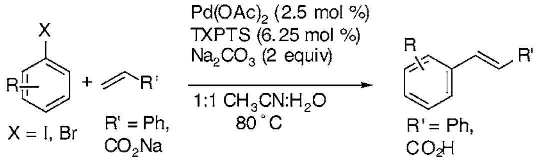
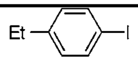
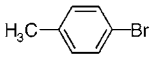
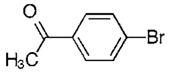
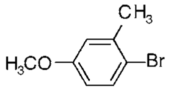
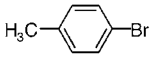
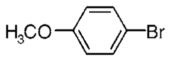
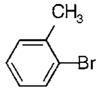
(13) Western, E. C.; Daft, J. R.; Johnson, E. M., II; Gannett, P. M.; Shaughnessy, K. H. *J. Org. Chem.* **2003**, *68*, 6767−6774.

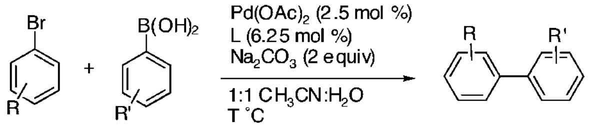
Table 1. Heck Coupling of Aryl Bromides with TXPTS/Pd(OAc)$_2$



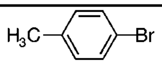
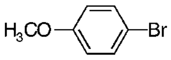
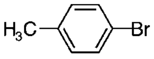
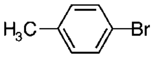
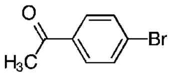
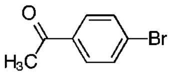
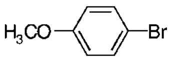
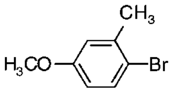
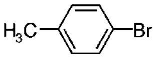
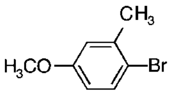
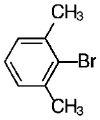
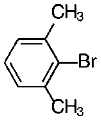
entry	ArBr	alkene	% yield[a]
1		styrene	90
2		styrene	90
3		styrene	94
4		styrene	78
5		Na acrylate	81
6		Na acrylate	79
7		Na acrylate	82

[a] See Supporting Information for experimental conditions.

Table 2. Scope of Suzuki Coupling with TXPTS or TMAPTS/Pd(OAc)$_2$

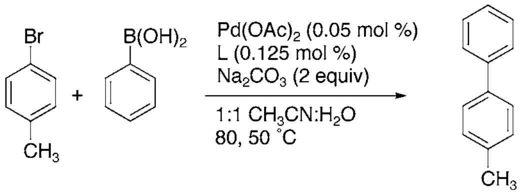


1a-d
a: R = H
b: R' = 4-F
c: R' = 4-MeO
d: R' = 2-Me

entry	aryl bromide	boronic acid	ligand	T (°C)	% yield[a]
1		**1 a**	TXPTS TMAPTS	80 50	98 95
2		**1 a**	TXPTS	80	99
3		**1 b**	TXPTS TXPTS	80 50	98 94
4		**1 c**	TXPTS TXPTS	80 50	92 92
5		**1 a**	TXPTS TXPTS	80 50	99 91
6		**1 c**	TMAPTS TMAPTS	80 50	90 93
7		**1 b**	TMAPTS	50	97
8		**1 a**	TXPTS TXPTS	80 50	97 88
9		**1 d**	TMAPTS TMAPTS	80 50	86 67
10		**1 d**	TXPTS TMAPTS TXPTS TMAPTS	80 80 50 50	92 91 75 85
11		**1 a**	TXPTS TXPTS	80 50	84 78
12		**1 b**	TMAPTS	50	87

[a] See Supporting Information for experimental conditions.

functionalized stilbenes. Introduction of an ortho substituent on the aryl halide resulted in a somewhat decreased yield of product (entry 4). Attempts to couple 2-bromo-*m*-xylene with styrene gave none of the desired product. Butyl acrylate was slowly hydrolyzed under the coupling conditions, but sodium acrylate gave good yields of cinnamic acid derivatives after acidic workup. Again both electron-rich and moderately sterically demanding aryl bromides gave good yields.



(2)

The activity of TXPTS and TMAPTS were next compared to that of TPPTS in a standard Suzuki coupling of a nonactivated aryl bromide, 4-bromotoluene, and phenylboronic acid using Pd(OAc)$_2$ (0.05 mol %), ligand (0.125 mol %), and sodium carbonate in a 1:1 mixture of water and acetonitrile (eq 2). At 80 °C, all ligands gave complete conversion within 1 h (Figure 2). Catalysts derived from Pd(OAc)$_2$ and the sulfonated phosphines were only slightly more active than Pd(OAc)$_2$ alone. At 50 °C, catalysts derived from TXPTS and TMAPTS gave higher yields than the catalyst derived from TPPTS. After 2.5 h, TXPTS gave a 78% yield (1600 mol product(mol Pd)$^{-1}$, TOF = 620 mol product(mol Pd•h)$^{-1}$) and TMAPTS gave a 68% yield (1400 mol product(mol Pd)$^{-1}$, TOF = 540 mol product(mol Pd•h)$^{-1}$), while TPPTS gave only a 48% yield (960 mol product(mol Pd)$^{-1}$, TOF = 380 mol product(mol Pd•h)$^{-1}$). After 5 h, the TXPTS system showed little additional

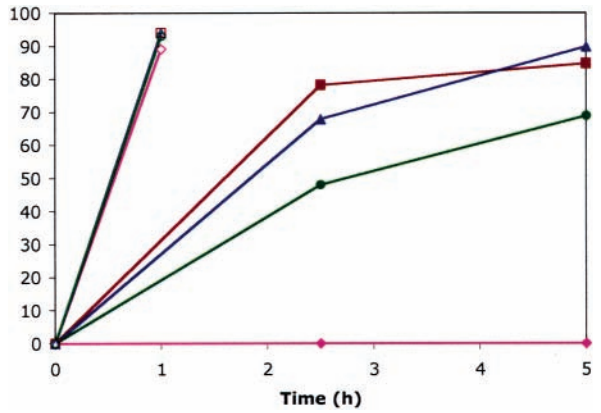


Figure 2. Comparison of L/Pd(OAc)$_2$ activity in the coupling of 4-bromotoluene and phenylboronic acid. □ = TXPTS, 80 °C; △ = TMAPTS, 80 °C; ○ = TPPTS, 80 °C; ◇ = no L, 80 °C; ■ = TXPTS, 50 °C; ▲ = TMAPTS, 50 °C; ● = TPPTS, 50 °C; ◆ = no L, 50 °C.

conversion, while both TMAPTS and TPPTS gave higher yields than after 2.5 h. After 5 h, the TMAPTS system gave a slightly higher yield than the TXPTS system. In the absence of ligand, no product was formed at 50 °C.

The scope of Suzuki couplings catalyzed by TXPTS and TMAPTS in combination with Pd(OAc)$_2$ (2.5 mol %) was tested for a variety of aryl bromide and arylboronic acid combinations (Table 2). Both ligands gave very similar results under these conditions. Excellent yields (90−99%) were obtained with sterically unhindered, electron-rich (entries 2 and 3) and electron-deficient (entries 5−7) aryl bromides. Similarly, boronic acids with electron-withdrawing (entry 3) or electron-donating substituents (entries 4 and 6) gave high yields. For these sterically unhindered substrates, similar yields were obtained at 50 and 80 °C.

Catalyst systems derived from TXPTS and TMAPTS do show some sensitivity to ortho substituents. Coupling 4-bromo-3-methylanisole and phenylboronic acid at 80 and 50 °C gave excellent yields of the coupling product (entry 8). Couplings of 2-tolylboronic acid with 4-bromotoluene using TMAPTS gave an 86% yield at 80 °C and a 67% yield at 50 °C (entry 9). Similarly, couplings to give a 2,2′-dimethylbiphenyl product occurred in excellent yield at 80 °C, but the yield dropped from 90 to 75 and 85%, respectively, for the TXPTS and TMAPTS systems at 50 °C (entry 10). 2-Bromo-*m*-xylene gave somewhat lower yields of 2,6-dimethyl-substituted biphenyl products (78−87% yield) at both 50 and 80 °C. Attempts to prepare 2,2′,6-trimethylbiphenyl from 2-bromo-*m*-xylene and *o*-tolylboronic acid were unsuccessful.

In conclusion, TXPTS in combination with palladium acetate provides active catalysts for Heck and Suzuki couplings of aryl bromides at modest temperatures. TXPTS is an air-stable ligand that can be prepared in two steps from PCl$_3$. While catalysts derived from TXPTS are only moderately more active than those derived from TPPTS for the Suzuki coupling, the TXPTS system provides a significant advantage in the Heck coupling of aryl bromides. Using TXPTS, we have achieved the first Heck couplings of unactivated and deactivated aryl bromides under relatively mild conditions in aqueous solvents.

Acknowledgment. We gratefully acknowledge financial support of this work by the National Science Foundation (CHE-0124255) and The University of Alabama through the School of Mines and Energy Development (SOMED) and the Research Activity Council. We thank Elizabeth C. Western, who prepared the TXPTS used in this work.

Supporting Information Available: Experimental details and compound characterization of TXPTS, TMAPTS, and compounds in Tables 1 and 2. This material is available free of charge via the Internet at http://pubs.acs.org.

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